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Preliminary communication

Stepwise degradation of moenomycin A

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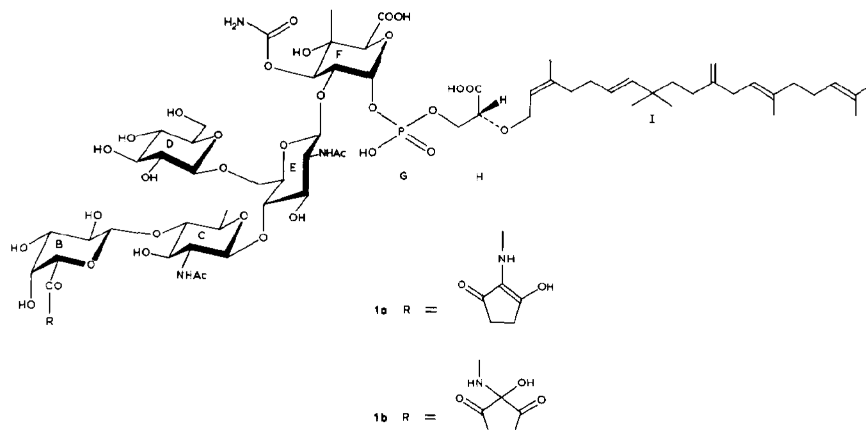
The antibiotic moenomycin A (**1a**) is the main constituent of the commercial product flavomycin® which is employed in animal nutrition[1]. Compound **1a** is an efficient inhibitor of the biosynthesis of peptidoglycans of bacterial cell-walls by interacting with the enzyme(s) that catalyse the transfer of the disaccharide unit from the disaccharide–(oligopeptide)–pyrophosphoryl–undecaprenol intermediate to the growing, linear peptidoglycan chain[2].

We now report on a systematic degradation of the oligosaccharide part of **1a** which was performed with the aim of defining the structural basis of the antibiotic activity of **1a**.



Transformation of **1a** to **3** by catalytic hydrogenation (to give **2**) and subsequent ozonolysis has already been described[3]. Compound **3** has now been obtained much more efficiently (88% yield) from **2** (7.4 mmol) by oxidation with $K_3[Fe(CN)_6]$ (80.8 mmol) in 0.37M K_2CO_3 and subsequent reversed-phase chromatography (HP 20, water–methanol gradient). We believe that an intermediate of type **1b** is involved in this reaction.

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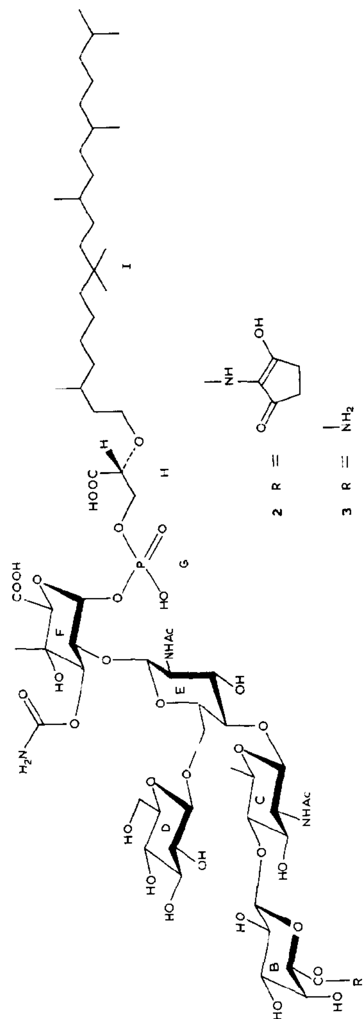
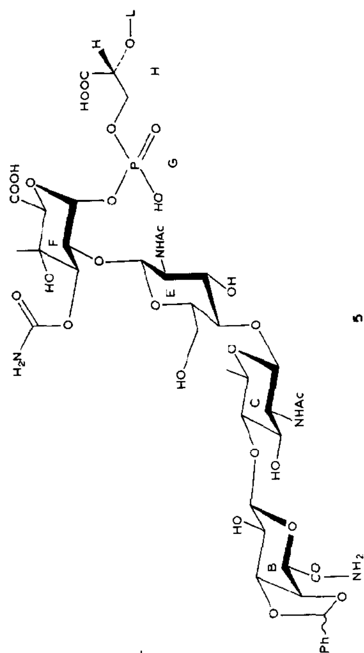

2 R =
3 R = NH2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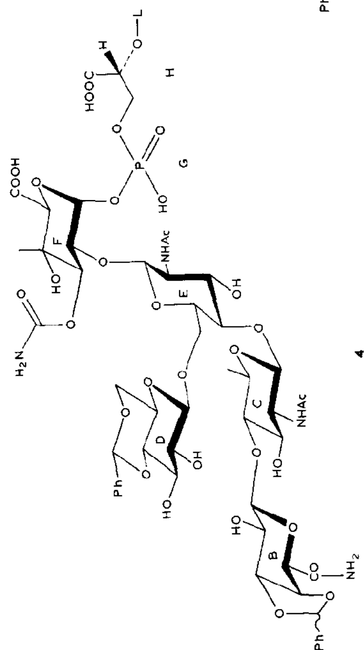
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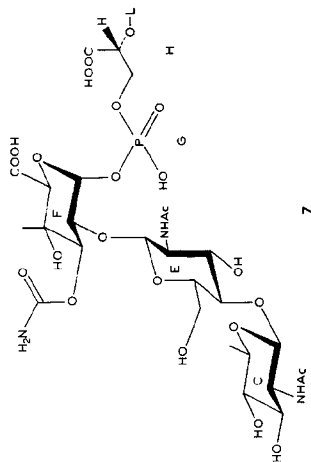

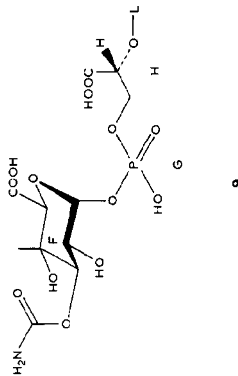

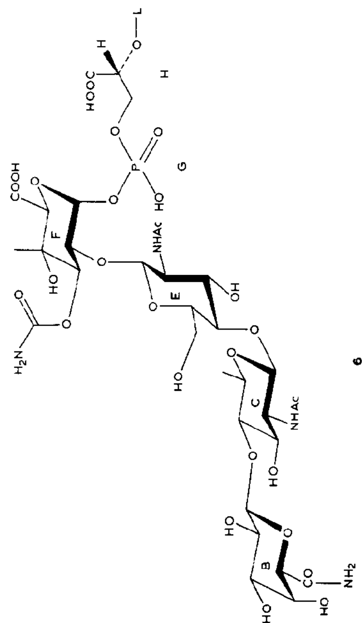

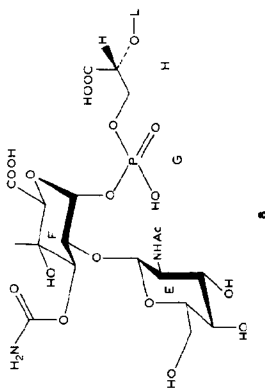

L = Lipid part (see unit I of 2)

Stepwise degradation of **3** was based on the diol-cleavage methodology[4]. Compound **3** (0.72 mmol) was treated for 52 h at 90° with benzaldehyde (28 mmol) and anhydrous zinc chloride (9.9 mmol) in dimethyl sulfoxide solution[5], to give, after chromatographic separations (first on HP-20 with a water–methanol gradient and then on silica gel with 10:6:1 chloroform–methanol–water), **4** in 14% yield; **4** is possibly a mixture of two diastereoisomers isomeric at the acetal carbon of the benzylidene group of unit B. Only unit D of **4** contains a free diol group. Therefore, (*a*) cleavage of **4** (0.12 mmol) with sodium metaperiodate (0.4 mmol) in 50% acetic acid containing sodium acetate (1.9 mmol) at 40° for 5 h, (*b*) reversed-phase chromatography (HP 20, water–methanol gradient) and lyophilisation, (*c*) reaction[6] (Barry degradation[7]) with a 100-fold excess of *N,N*-dimethylhydrazine in 2-propanol–M H_2SO_4 at pH 4 (2.5 h at 20° and 1 h at 90°), and (*d*) lyophilisation and chromatographic separation (silica gel, 10:6:1 chloroform–methanol–water) gave **5** in 37% overall yield.

Liberation of another diol grouping was achieved by removing the benzylidene group from **5** by hydrogenolysis (in 1:8 methanol–acetic acid, Pd/C catalyst) to give **6** quantitatively. Degradation under the conditions described above converted **6** into **7** (32%).

TABLE I

SELECTED ^{13}C-N.M.R. DATA [δ VALUES, $(CD_3)_2SO$] FOR COMPOUNDS 3–9

3	4	5	6	7	8	9	*Assignment*	*Unit*
173.1	171.6	172.5	[a]	173.3	173.3	[a]	C-1	H
171.7	171.3	171.8	171.6	171.7	172.1	172.6	C-6	F
170.6	170.6	169.6	170.7	–	–	–	C-6	B
169.7	169.7	169.2	169.3	169.4	169.4	–	$NHCOCH_3$	C,E
156.5	156.7	156.6	156.7	156.6	156.3	158.0	$OCONH_2$	F
103.6	104.2	–	–	–	–	–	C-1	D
102.9	103.7	102.8	103.8	–	–	–	C-1	B
101.9	102.9	102.3	102.5	102.7	102.9	–	C-1	E
101.2	102.5	101.7	101.5	101.9	–	–	C-1	C
–	101.5	101.3	–	–	–	–	C-7[b]	B
–	101.0	–	–	–	–	–	C-7[b]	D
93.7	94.3	93.8	94.1	94.2	94.3	94.5	C-1	F
84.4	84.8	84.6	84.4	75.4	–	–	C-4	C
80.7	80.7	80.7	80.8	80.4	70.5	–	C-4	E
71.9	70.8	70.8	59.6	59.2	60.7	–	C-6	E
70.3	80.7	80.7	70.5	–	–	–	C-4	B
69.0	80.7	–	–	–	–	–	C-4	D
55.5	55.7	55.5	55.5	55.5	55.1	–	C-2	E
55.0	54.6	54.6	54.3	54.3	–	–	C-2	C
23.1	23.4	[a]	23.4	23.2	23.3	–	$NHCOCH_3$	C,E
17.3	17.3	17.4	17.4	18.0	–	–	C-6	C
16.2	16.2	16.3	16.4	16.4	16.9	16.7	CH_3-4	F

[a] Not observable. [b] Acetal carbon.

The tetrasaccharide **7** could be obtained from **3** directly by removing units B and D in one step. Thus, (*a*) cleavage of **3** (0.7 mmol) with an excess of sodium metaperiodate (4.7 mmol) in 50% acetic acid containing sodium acetate (7.3 mmol) for 2 h at 40°, (*b*) reversed-phase chromatography (HP 20, water–methanol gradient) and lyophilisation, (*c*) treatment of the oxidation product with a 20-fold excess of *N,N*-dimethylhydrazine in 2-propanol–M H_2SO_4 (pH 4.5) for 3 h at 85°, and (*d*) chromatographic separation (first on HP 20 with a water–methanol gradient and then on silica gel with 10:6:1 chloroform–methanol–water) furnished **7** in a 47% overall yield. Compound **7** could be submitted to another degradation cycle in which ammonia was used instead of *N,N*-dimethylhydrazine[8]. Thus, (*a*) treatment of **7** (0.4 mmol) with sodium metaperiodate (1.6 mmol) under the conditions described above, (*b*) destruction of the excess of periodate with 1.9 mmol of ethylene glycol (1 h at 20°), (*c*) degradation of the oxidation products with ammonia (pH 9.5, 16 h at 20°), (*d*) adjustment to pH 6 and chromatographic separations (HP 20, water–methanol gradient; and then silica gel, 10:6:1 chloroform–methanol–water) gave **8** (31%) and **9** (16%). Under the same conditions, **8** was degraded to **9** in 46% yield. All new compounds gave spectra that were in agreement with the assigned structures. The most characteristic and informative ^{13}C-n.m.r. signals are collected in Table I.

In the *in vitro* assay[2] for the transglycosylation step, moenomycin A (**1a**), **2**, **3**, and the degradation products **6**–**8** showed the same inhibitory effect, whereas **9** was 10-fold less efficient. From these results, it is concluded that only units E, F, G, H, and I of **1a** are essential for full biological (*in vitro*) activity.

ACKNOWLEDGMENTS

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